Remarks

Applicants appreciate the thorough examination of the present application as evidenced by the Office Action mailed March 20, 2002. Applicants further appreciate the withdrawal of the restriction requirement of Paper No. 3 with respect to Claim 23. Claims 12-15 and 17-25 are pending in the present application.

The Action requests appropriate correction where trademarks are used in the application. Claims 12-15 and 17-25 stand rejected under 35 U.S.C. § 112, first paragraph, Claims 12-15 and 17-25 stand rejected under 35 U.S.C. § 112, second paragraph, Claims 12-15, 21, and 23-25 stand rejected under 35 U.S.C. § 102(b), and Claims 12-15 and 17-25 stand rejected under 35 U.S.C. § 103. Applicants address each of these requests or rejections below.

I. Trademark Correction

The Action notes that trademarks should be capitalized and accompanied by the generic terminology. Applicants have submitted replacement paragraphs in which the trademarks have been capitalized and are accompanied by generic terminology. Applicants respectfully comply with this requirement.

II. Claim Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 12-15 and 17-25 stand rejected under 35 U.S.C. § 112, first paragraph. More specifically, the Action states,

> [B]ecause the specification, while being enabling for a method of treating a solid, vascularized tumor with a chemotherapeutic agent, cisplatin, does not reasonably provide enablement for a method of treating a solid vascularized tumor with a chemotherapeutic in combination with erythropoietin.

Action, page 3. Applicants respectfully traverse this rejection.

The Court of Appeals for the Federal Circuit has articulated the test of enablement in terms of "whether one skilled in the art could make or use the invention from the disclosures in

the patent coupled with information known in the art without undue experimentation." United States v. Telectronics, Inc., 8 U.S.P.Q.2d 1217, 1223 (Fed. Cir. 1988). In *In re Wands*, the Federal Circuit enumerated factors to be considered in determining whether a disclosure would require undue experimentation. *In re* Wands, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988) (citing *Ex parte* Forman, 230 U.S.P.Q. 546, 547 (1986)). These factors include, but are not limited to, the following:

(1) The quantity of experimentation necessary;
(2) The amount of direction or guidance presented;
(3) The presence or absence of working examples;
(4) The nature of the invention;
(5) The state of the prior art;
(6) The relative skill of those in the art;
(7) The predictability or unpredictability of the art; and
(8) The breadth of the claims.

Wands, 8 U.S.P.Q.2d at 1404; *See also* MANUAL OF PATENTING EXAMINING PROCEDURE § 2164.01(a) (7th ed. rev. 1, 2000).

Applicants note that, in this case, one skilled in the art is one skilled in the areas of clinical research and/or medicine. Moreover, one skilled in these areas would be familiar with aspects of oncology, chemotherapy agents and regimens, and/or cardiology. As such, Applicants respectfully submit that one skilled in these areas would not be forced to exercise undue experimentation in order to practice the claimed invention. Instead, one skilled in these particular arts would possess the expertise and experience in clinical research and/or medicine that would enable the artisan to apply the teachings of the present invention to make determinations regarding patient care on an individual patient basis as is typical of medical care provided to patients in need of such treatment. Thus, in view of the level of skill of those in the art, the disclosure provided in the present application, including examples, and the common

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practice of developing treatment protocols to suit the needs of the specific patient, Applicants submit that one skilled in the art pertinent to this invention would not be forced to exercise undue experimentation in order to determine which mode (i.e., dosage and treatment protocol) of administration would be most appropriate for treating a vascularized solid tumor. Accordingly, Applicants respectfully request that the rejection of Claims 12-15 and 17-25 under 35 U.S.C. § 112, first paragraph be withdrawn.

III. Rejection under 35 U.S.C. § 112, Second Paragraph

Claims 12-15 and 17-25 stand rejected under 35 U.S.C. § 112, second paragraph. More specifically, the Action states that these claims are indefinite because "claim 12 recites the phrase 'an endothelial-inhibiting amount.' The claims are confusing because it is not clear what is being inhibited . . . . Further, the term "inhibiting" is a relative term which is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention." Action, page 10. Applicants respectfully traverse this rejection.

Applicants clearly define "endothelial-inhibiting amount" in the specification at page 6, lines 19-31 by stating the following:

> endothelial-inhibiting amounts of EPO refer to those **dosages which enhance or increase the suppression of endothelial growth which would otherwise occur due to exposure to a chemotherapeutic agent or radiation, mechanical trauma, or a disease state known to damage the endothelium**. Alternatively, an endothelial-inhibiting amount of EPO may be defined as those **dosages which decrease the numbers of viable endothelial cells following exposure to the chemotherapeutic agent or radiation, mechanical trauma, or a disease state known to damage the endothelium; the decreased number of viable cells is in comparison to that which would be expected in the absence of EPO.** (Emphasis added).

Thus, as used in the present application, endothelial-inhibiting amounts refer to dosages which enhance or increase suppression of endothelial growth in response to the conditions described

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above, or dosages which decrease the numbers of viable endothelial cells in response to the conditions described above. Moreover, Applicants note that the term "inhibiting" as used in the present application is commensurate with its ordinary meaning as known by those skilled in the art. For example, the McGraw-Hill Dictionary of Scientific and Technical Terms (3d edition) (1984) provides a definition of "inhibition" as "the act of repressing or restraining a physical or chemical action." Thus, "inhibiting amount" may refer to an amount resulting in the repression or restraint of a physical or chemical action. In the present case, the repression or restraint relates to endothelial growth and/or the number of viable endothelial cells as described in the present application. Therefore, Applicants submit that Claim 12 is not unclear based upon the recitation "an endothelial-inhibiting amount." Accordingly, Applicants respectfully request that the rejection of Claims 12-15 and 17-25 under 35 U.S.C. § 112, second paragraph be withdrawn.

IV. Claim Rejections Under 35 U.S.C. § 102

Claims 12-15, 21, and 23-25 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Platanias et al., *J. Clin. Oncol*, 9:2021-2026 (1991). Applicants respectfully traverse this rejection.

"Anticipation under 35 U.S.C. § 102 requires the disclosure in a single piece of prior art of each and every limitation of a claimed invention." *Apple Computer Inc. v. Articulate Systems Inc.* 57 USPQ2d 1057, 1061 (Fed. Cir. 2000) (*relying on Electro Med. Sys. S.A. v. Cooper Life Scis.*, 32 USPQ2d 1017, 1019 (Fed Cir. 1994). Additionally, a finding of anticipation further requires that there must be no difference between the claimed invention and the disclosure of the cited reference as viewed by one of ordinary skill in the art. *See Scripps Clinic & Research Foundation v. Genentech Inc.*, 927 F.2d 1565, 1576, 18 U.S.P.Q.2d 1001, 1010 (Fed. Cir. 1991).

Applicants note that Platanias et al. disclose treatment of **chemotherapy-induced anemia** with recombinant human erythropoietin in cancer patients. In contrast, in one embodiment, the present invention relates to a method of treating a **solid vascularized tumor**, among other things, as recited in Claims 12 and 21. Moreover, as described in the present application, "[t]he use of EPO to enhance endothelial growth-suppression during chemotherapy is

useful in treating angiogenic tumors, where it is desirable to prevent or slow the formation of new blood vessels which support tumor growth. Tumors require an adequate blood supply, and growth of new vessels in the tumor mass is stimulated by angiogenic factors secreted by tumor tissue." Present Application, page 4 lines 16-20. Thus, where Platanias teaches treatment of chemotherapy-induced anemia, the present invention, in some aspects, relates to treatment of solid vascularized tumors. Therefore, Platanias et al. does not disclose each and every element of the claimed invention, and clear differences exist between Platanias et al. and the present invention. Accordingly, Applicants respectfully request that the rejection of Claims 12-15, 21, and 23-25 under 35 U.S.C. § 102(b) be withdrawn.

V. Claim Rejections Under 35 U.S.C. § 103

Claims 12-15 and 17-25 stand rejected under 35 U.S.C. § 103 as being unpatentable over Platanias et al. and further in view of Markham et al., *Drugs*, 49:232-254 (1995) and also Wood et al., *J. Clin. Invest.* 95: 1650-1659 (1995). More specifically, the Action states the following:

> It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have substituted the cisplatin of Markham et al. for one of the chemotherapeutic agents of Platanias et al. because Platanias et al. specifically teach the treatment of solid tumors with chemotherapeutic agents and Markham et al. teach the treatment of solid tumors with cisplatin, a therapeutic agent. One would have a reasonable expectation of success for substituting the cisplatin of Markham et al. for the chemotherapeutic agents of Platanias et al. because cisplatin is a well known chemotherapeutic agent. Further, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made and one would have been motivated to deliver the cisplatin intravenously because Wood et al. teach the conventional administration of cisplatin to cancer patients by intravenous administration.

Action, page 14. Applicants respectfully traverse this rejection.

The cited reference or references when combined must teach or suggest *all* the recitations of the claims, and there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. *See* M.P.E.P. §2143. The mere fact that

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references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *See* M.P.E.P. §2143.01, relying on *In re Mills*, 916 F.2d 680, 16 U.S.P.Q.2d 1430 (Fed. Cir. 1990).

In the present case, the cited references either alone, or in combination, fail to suggest all the claim recitations of the present invention. As described in detail above, in one embodiment, the present invention relates to a method of **treating a solid vascularized tumor**, among other things, as recited in Claims 12 and 21. In contrast, the cited references, in some form, relate to **treating chemotherapy-induced anemia**. Thus, none of the cited references disclose or suggest treating a solid vascularized tumor.

Applicants also note that no motivation exists to combine these cited references, and even if combined, the cited references do not teach or suggest the present invention. As previously noted, these references relate to treating chemotherapy-induced anemia and not treating a solid vascularized tumor, among other things, as recited in Claims 12 and 21. Thus, one could not arrive at the present invention even if Platanias et al., Markham et al., and Wood et al. were combined. Therefore, it would not have been *prima facie* obvious to one skilled in the art to combine the cited references to arrive at the present invention. Accordingly, Applicants respectfully request that the rejection of Claims 12-15 and 17-25 under 35 U.S.C. § 103 be withdrawn.

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VI. Conclusion

In view of the foregoing remarks, Applicants respectfully request that all outstanding rejections to the claims be withdrawn and that a Notice of Allowance be issued in due course. Any questions that the Examiner may have should be directed to the undersigned, who may be reached at (919) 854-1400.

Respectfully submitted,

Kenneth D. Sibley
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I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, Washington, DC 20231 on June 20, 2002.

Vickie Diane Prior
Date of Signature: June 20, 2002

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Version With Markings To Show Changes Made

In the Specification:

Please replace the paragraph at page 1, line 11 through page 2, line 3 with the following replacement paragraph:

Erythropoietin (EPO) is a glycoprotein produced in the kidney, and is the principal hormone responsible for stimulating red blood cell production (erythrogenesis). EPO stimulates the division and differentiation of committed erythroid progenitors in the bone marrow. Normal plasma erythropoietin levels range from 0.01 to 0.03 Units/mL, and can increase up to 100 to 1,000-fold during hypoxia or anemia. Graber and Krantz, *Ann. Rev. Med.* 29:51 (1978); Eschbach and Adamson, *Kidney Intl.* 28:1 (1985). Recombinant human erythropoietin (rHuEpo or epoetin alfa) is commercially available as [Epogen®] EPOGEN® (Amgen Inc., Thousand Oaks, CA) and as [Procrit®] PROCRIT® (Ortho Biotech Inc., Raritan, NJ). EPO is indicated for treatment of anemia, including anemias associated with cancer chemotherapy, chronic renal failure, malignancies, adult and juvenile rheumatoid arthritis, disorders of haemoglobin synthesis, prematurity, and zidovudine treatment of HIV infection.

Please replace the paragraph at page 8, line 5 through line 33 with the following replacement paragraph:

As used herein, human erythropoietin (EPO) refers to both the naturally occurring human erythropoietin glycoprotein as well as recombinant human erythropoietin (rHuEpo or epoetin alfa, available commercially as [Epogen®] EPOGEN® (Amgen Inc., Thousand Oaks, CA) and as [Procrit®] PROCRIT® (Ortho Biotech Inc., Raritan, NJ)). Peptide analogs of EPO may also be used in the methods of the present invention. As used herein, peptide analogs are those compounds which, while not having amino acid sequences identical to that of EPO, have a similar three-dimensional structure. In protein molecules which interact with a receptor, the interaction takes place at the surface-accessible sites in a stable three-dimensional molecule. By arranging the

critical binding site residues in an appropriate conformation, peptides which mimic the essential surface features of EPO binding region may be designed and synthesized in accordance with known techniques. A molecule which has a surface region with essentially the same molecular topology to the binding surface of EPO will be able to mimic the interaction of EPO with the EPO receptor. Methods for determining peptide three-dimensional structure and analogs thereto are known, and are sometimes called 'rational drug design techniques'. *See, e.g.,* U.S. Patent No. 4,833,092 to Geysen; U.S. Patent No. 4,859,765 to Nestor; U.S. Patent No. 4,853,871 to Pantoliano; U.S. Patent No. 4,863,857 to Blalock (applicants specifically intend that the disclosures of all U.S. patents cited herein be incorporated by reference in their entirety).

Please replace the paragraph at page 9, line 31 through page 10, line 22 with the following replacement paragraph:

Exemplary chemotherapeutic agents are vinca alkaloids, epipodophyllotoxins, anthracycline antibiotics, actinomycin D, plicamycin, puromycin, gramicidin D, paclitaxel ([Taxol®] TAXOL®, Bristol Myers Squibb), colchicine, cytochalasin B, emetine, maytansine, and amsacrine (or "mAMSA"). The vinca alkaloid class is described in Goodman and Gilman's The Pharmacological Basis of Therapeutics, 1277-1280 (7th ed. 1985) (hereafter "Goodman and Gilman"). Exemplary of vinca alkaloids are vincristine, vinblastine, and vindesine. The epipodophyllotoxin class is described in Goodman and Gilman, supra at 1280-1281. Exemplary of epipodophyllotoxins are etoposide, etoposide orthoquinone, and teniposide. The anthracycline antibiotic class is described in Goodman and Gilman, supra at 1283-1285. Exemplary of anthracycline antibiotics are daunorubicin, doxorubicin, mitoxantraone, and bisanthrene. Actinomycin D, also called Dactinomycin, is described in Goodman and Gilman, supra at 1281-1283. Plicamycin, also called mithramycin, is described in Goodman and Gilman, supra at 1287-1288. Additional chemotherapeutic agents include cisplatin ([Platinol®] PLATINOL®, Bristol Myers Squibb); carboplatin ([Paraplatin®] PARAPLATIN®, Bristol Myers Squibb); mitomycin ([Mutamycin®] MUTAMYCIN®, Bristol Myers Squibb); altretamine ([Hexalen®] HEXALEN®,

U.S. Bioscience, Inc.); cyclophosphamide ([Cytoxan®] CYTOXAN®, Bristol Myers Squibb); lomustine [CCNU] ([CeeNU®] CEENU®, Bristol Myers Squibb); carmustine [BCNU] ([BiCNU®] BICNU®, Bristol Myers Squibb).